REMARKS/ARGUMENTS

This Amendment and Remarks are in response to the Office Action dated April 9, 2007. Reconsideration of this application and entry of this amendment is respectfully requested.

Claims 1-17 and 20-29 are pending in this application. Claims 3-6 and 12-17 have been withdrawn as the result of an earlier restriction requirement without prejudice to Applicant's right to pursue the subject matter of the withdrawn claims in one or more related applications. Claims 18-19 were previously cancelled.

Claims 30 and 31 have been added to further define and claim that which Applicants consider their invention. Support for claim 30 can be found in originally filed claim 27. Support for claim 31 can be found in the specification in Figure 9 and in Example 3. No new matter has been added as a result of the claim amendments.

By the amendments, Applicants do not acquiesce to the propriety of any of the Examiner's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

Rejections Under 35 U.S.C. §103

To reject a claim under 35 U.S.C. §103(a), the Examiner bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. *In re Bell*, 26 USPQ.2d 1529 (Fed. Cir. 1992). If the Examiner cannot establish a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent. *In re Oetiker*, 24 USPQ.2d 1443 (Fed Cir. 1992).

The rejection of claims 1-2, 7-11 and 20 under 35 U.S.C. §103(a) as being unpatentable over Hooper et al. and Thomson et al. has been maintained.

Applicants respectfully traverse. Independent claims 1, 8, and 20 have been amended to include the language "wherein each of said external immunogen comprises

a portion of said membrane-associated protein comprising the external epitopes." Support for this language can be found in the specification in paragraph 0020 which states that "'[a]n external immunogen' as used herein refers to surface immunogens that are generally unhindered by obscuring structures or compositions. For example, the external immunogens of the present invention are viral antigens expressed on the surface of the virus particle (virion) and thus exposed to a host's immune system unhindered." Claim 1 has been amended further to include external immunogens of "at least two" membrane associated proteins of variola major or immunologically cross-reactive poxviruses. Support for this claim amendment can be found in originally filed claim 8. Claim 10 has been amended to incorporate the elements of claim 11. Claim 11 has been canceled. No new matter has been added to the claims as a result of these amendments.

Hooper teaches an immune globulin composition comprising one or more monoclonal antibodies against vaccinia antigens (paragraph 0005) wherein the monoclonal antibodies are neutralizing antibodies and further teaches methods of generating neutralizing antibodies by immunizing with vaccinia antigens. Hooper also teaches the vaccinia gene products L1R and A33R as preferred antigens for generating neutralizing antibodies. Hooper does not teach or suggest the claimed polyproteins or immunogenic compositions comprised of such polyproteins. The Examiner has stated on page 3, first paragraph of the Office Action of April 9, 2007 that "Hooper teaches that the immunogen can be administered with adjuvants or as a fusion protein to induce an immune response and that fusion proteins comprise the peptide against which an immune response is desired coupled to carrier proteins (page 3, paragraph 022)" and that "Hooper teaches about fusion proteins which are polyproteins, therefore Hooper teaches polyproteins". Applicants respectfully disagree. The instant claims have been amended to clarify that the polyprotein contains external immunogens of *at least two* membrane associated proteins of variola major. Hooper does not disclose polyproteins containing external immunogens of at least two membrane associated proteins of variola major. The carrier proteins taught by Hooper are b-galactosidase, glutathione-S-transferase, keyhole limpet hemocyanin and bovine serum albumin. None of these

carrier proteins are external immunogens of membrane associated proteins of variola major or immunologically cross-reactive poxviruses.

The deficiencies of Hooper are not remedied by Thomson. Thomson teaches the delivery of multiple epitope DNA vaccines for the induction of cytotoxic T lymphocyte (CTL) responses. Thomson teaches DNA vaccines comprising "polytopes" which Thomson defines as comprising a series of minimal CTL epitopes, the DNA encoding the epitopes comprising only the epitope sequence and not any other portion of the gene of interest (page 171, column 2, first paragraph continued from column 1). Furthermore, Figure 1B of Thomson depicts the amino acid sequence of a polytope, which is described in the figure legend as "10 contiguous CD8 epitopes". As depicted in Figure 1B, none of the epitope sequences includes more than ten amino acids. Thomson does not teach or suggest polyproteins, particularly polyproteins comprising external immunogens of at least two membrane associated proteins wherein each of the external immunogens comprise a portion of the the membrane-associated protein comprising the external epitopes. Furthermore, Thomson teaches epitope-based CTL vaccines only for EBV, HIV and certain cancers, and in fact the vaccines of Thomson include epitopes for multiple different viruses, parasites and tumors in the same vaccine. The instant claims have been amended by inclusion of the element "wherein each of said external immunogen comprises a portion of said membrane-associated protein comprising the external epitopes" and therefore the amended claims exclude the polytope design disclosed by Thomson.

On page 4 of the Office Action of April 9, 2007, the Examiner rebuts Applicants arguments presented in the previous response. Although the claims as amended overcome the rejection Applicant nonetheless wishes to address the Examiner's comments. Applicants argued that there was no expectation of success to combine the teachings of Hooper (generating neutralizing monoclonal antibodies to vaccinia-associated proteins in mice) with the teachings of Thomson (epitope-based CTL vaccine to yield polyprotein-based immunogenic vaccines for poxviruses. The Examiner asserted that because Hooper teaches drawbacks to vaccinia immune globulin and need for a safe and effective immune globulin, there is a reasonable

expectation of success for a person or ordinary skill in the art to combine Hooper and Thomson to obtain a polyprotein comprising external immunogens of membrane-associated proteins of variola major or immunologically cross-reactive poxviruses. Applicants assert that the claimed invention is not drawn to immune globulin, a passive immunization product, but rather the production of vaccines to actively induce a protective or therapeutic immune response in a subject. Applicants respectfully assert that Hooper and Thomson are non-analogous art because Thomson teaches active immunization for CTL, not for antibodies. CTL responses require short peptides (epitopes) in context of MHC proteins not in context of the native protein, thus there is a reasonable expectation of success that a polytope will successfully induce a CTL response to at least a subset of its constituent epitopes. In contrast, neutralizing antibodies generally recognize epitopes only in context of the native structure of the protein. Since a polytope construct will not maintain this native context there can be no expectation of success that such a polytope construct will induce a neutralizing antibody response. Therefore, Applicants reassert the argument that there is no expectation of success to combine the teachings of Hooper (generating neutralizing monoclonal antibodies to vaccinia-associated proteins in mice) with the teachings of Thomson (epitope-based CTL vaccine) to yield polyprotein-based immunogenic vaccines for poxviruses.

Furthermore, polyprotein and polyepitope (or polytope) are established terms of art with distinct, non-overlapping meanings. Thomson teaches polytopes and does not teach polyproteins. Hooper does not teach polyproteins within the scope of the amended claims. Therefore, regardless of whether Hooper and Thomson are analogous art, the combination of Hooper and Thomson does not teach or suggest every element of the claims.

Based on the foregoing, Applicants respectfully submit that Hooper and Thomson, in combination, do not teach or suggest each and every element of amended claims 1-2, 7-10 and 20 namely, a polyprotein comprising external immunogens of at least two membrane-associated proteins of variola major or immunologically cross-reactive poxviruses, wherein each of the external immunogens comprises a portion of

the membrane-associated protein comprising the external epitopes. Furthermore, there is no reasonable expectation of success to generate the presently claimed invention based on the combination teachings of Hooper and Thomson. Therefore the Examiner has not established *prima facie* obviousness of claims 1-2, 7-10 and 20 based on Hooper in view of Thomson. Accordingly, Applicant respectfully submits that claims 1-2, 7-10 and 20 are not obvious under 35 USC §103(a) over the cited prior art and request the withdrawal of the outstanding rejection on this basis.

The rejection of claim 21 under 35 U.S.C. §103(a) as being unpatentable over Hooper et al. in view of Thomson et al. and further in view of Curiel et al. has been maintained.

Applicants respectfully traverse. It has been argued *supra* that claim 20 is not *prima facie* obvious over Hooper in view of Thomson because these references do not teach or suggest each and every element of independent claim 20 and there is not a reasonable expectation of success from combining these references. Claim 21 depends from claim 20 and thus incorporates all the elements of claim 20.

The deficiencies of Hooper and Thomson as invalidating 35 U.S.C. §103(a) art are not remedied by Curiel. Curiel teaches viral conjugates wherein the virus and a nucleic acid binding domain are bound by a biotin-streptavidin bridge.

The combination of Hooper, Thomson and Curiel do not teach or suggest all the elements of claim 21, specifically immunogenic compositions comprised of complexes of polypeptides wherein each polypeptide comprises an external immunogen of a membrane-associated protein of variola major or immunologically cross-reactive poxviruses, wherein each of the external immunogen comprises a portion of the membrane-associated proteins comprising the external epitopes and wherein the polypeptides are biotinylated and the complex is formed by the additional of avidin or streptavidin.

Therefore Applicants respectfully submit that the cited references, in combination, do not teach or suggest each and every element of claim 21 and therefore the Examiner has not established *prima facie* obviousness of claim 21 based on Hooper

in view of Thomson and Curiel and request the withdrawal of the outstanding rejection on this basis.

The rejection of claim 22 under 35 U.S.C. §103(a) as being unpatentable over Hooper et al. in view of Thomson et al. and further in view of Rutter et al. has been maintained.

Applicants respectfully traverse. It has been argued *supra* that claim 20 is not *prima facie* obvious over Hooper in view of Thomson because these references do not teach or suggest each and every element of independent claim 20 and there is not a reasonable expectation of success from combining these references. Claim 22 depends from claim 20 and thus incorporates all the elements of claim 20.

The deficiencies of Hooper and Thomson as invalidating 35 U.S.C. §103(a) art are not remedied by Rutter. Rutter teaches agents to facilitate the delivery of a viral subunit vaccine wherein the agent is a liposome.

The combination of Hooper, Thomson and Rutter do not teach or suggest all the elements of claim 22, specifically immunogenic compositions comprised of complexes of polypeptides wherein each polypeptide comprises an external immunogen of a membrane-associated protein of variola major or immunologically cross-reactive poxviruses, wherein each of the external immunogens comprises a portion of the membrane-associated protein comprising the external epitopes and wherein the complex is formed by anchoring the polypeptides in a liposome or micelle.

Therefore Applicants respectfully submit that the cited references, in combination, do not teach or suggest each and every element of claim 22 and therefore the Examiner has not established *prima facie* obviousness of claim 22 based on Hooper in view of Thomson and Rutter and request the withdrawal of the outstanding rejection on this basis.

The rejection of claims 23-26 under 35 U.S.C. §103(a) as being unpatentable over Hooper et al. in view of Thomson et al. and further in view of Newton et al. has been maintained for claims 23-26 and further for claims 27-29.

Applicants respectfully traverse. Hooper and Thomson have been discussed *supra*.

The deficiencies of Hooper and Thomson as invalidating 35 U.S.C. §103(a) art are not remedied by Newton. Newton teaches linkers to link peptides wherein the linkers include a $(GGGGS)_3$ linker. Newton also teaches affinity tags.

The combination of Hooper, Thomson and Newton does not teach or suggest all the elements of independent claims 23 and 29, specifically a polyprotein comprising external immunogens of at least two membrane-associated proteins of variola major or immunologically cross-reactive poxviruses wherein the individual proteins are jointed through a linker-spacer peptide and wherein each of the external immunogens comprises a portion of the membrane-associated proteins comprising the external epitopes.

Furthermore, the combination of Hooper, Thomson and Newton does not teach or suggest all the elements of claim 27 and 28, specifically wherein at least two of said immunogens comprises a polypeptide or protein selected from the group consisting of external immunogens and complete proteins wherein each of the external immunogen comprises a portion of themembrane-associated protein comprising the external epitopes.

Therefore Applicant respectfully submits that the cited references, either singly or in combination, do not teach or suggest each and every element of claims 23-29 and therefore the Examiner has not established *prima facie* obviousness of claims 23-29 over Hooper in view of Thomson and Newton.

Rejections Under 35 U.S.C. §112

Claims 27 and 28 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

The Examiner has stated that the term "consensus sequence" refers to a genus. Without agreeing to the propriety of the Examiner's rejection, Applicants have amended claims 27 and 28 to refer to a "consensus sequence" rather than a "variola consensus sequence." The consensus sequences obtained using the methods of claims 27 and 28 are disclosed in Figures 3-8 of the instant application. Six examples of consensus sequences are disclosed in the instant application. Applicants respectfully disagree with the Examiner's rejection on this basis. As the Examiner stated, a description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court indicated that, while applicants are not required to disclose every species encompassed by the genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. Because six species of this genus have been disclosed, Applicants respectfully assert that the genus was disclosed and Applicants are in possession of the invention as presently claimed. Therefore, Applicants respectfully request that the 35 U.S.C. §112 rejection of claims 27 and 28 on this basis be withdrawn.

Claim 10 has been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Claim 10 has been amended to incorporate the elements of claim 11. Claim 11, which depends from claim 10, was not rejected under 35 U.S.C. §112, first paragraph. Therefore, Applicants respectfully request that the 35 U.S.C. §112 rejection of claim 10 on this basis be withdrawn.

Conclusion

Applicants respectfully assert that the presently pending claims are in condition for allowance and request that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

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